

**REMARKS**

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

Claim 37 has been amended. Support for the amendment is found in the present application at, *e.g.*, paragraphs [0055], [0059], and [0065]–[0066]. No new matter has been added. Claims 37–40 are pending.

The rejection of claims 37–40 under 35 U.S.C. § 112 (1<sup>st</sup> para.) for lack of enablement is respectfully traversed in view of the above amendments.

The present claims relate to a method for identifying a compound that potentially induces the perception of a bitter taste. This method involves (i) contacting an isolated cell expressing the TRP8 channel protein of SEQ ID NO: 4 with a test compound and measuring the level of TRP8 activation; (ii) in a separate experiment, contacting an isolated cell expressing the TRP8 channel protein of SEQ ID NO: 4 with a vehicle control and measuring the level of TRP8 activation where the conditions are essentially the same as in part (i); and (iii) comparing the level of activation of TRP8 measured in part (i) with the level of activation of TRP8 in part (ii). An increased level of activated TRP8 in the presence of the test compound indicates that the test compound potentially induces the perception of a bitter taste.

The United States Patent and Trademark Office (“PTO”) has taken the position that this method is not enabled for two reasons: the skilled artisan would allegedly have no way of knowing whether a change in membrane potential was related to TRP8 activation, and, since TRP8 is involved in both sweet and bitter taste transduction, a test compound that results in TRP8 activation is not necessarily a bitter tastant. Applicants respectfully disagree that the claimed method is not enabled.

The PTO’s position is, essentially, that a positive test result in the claimed method does not necessarily mean that a test compound is an inducer of bitter taste. However, the present claims are directed to a method of identifying a compound that *potentially* induces the perception of a bitter taste. Accordingly, any rejection based on the claimed method’s supposed failure to *definitively* identify bitter taste inducers is not on point.

Additionally, the claimed method does identify compounds that potentially induce the perception of a bitter taste. As noted in applicants’ response filed September 21, 2006, the present application teaches at, *e.g.*, paragraphs [0008], [0038], and [0055], that

TRP8 participates in the taste signal transduction pathway and can be used to identify compounds that potentially induce the perception of a bitter taste. This is confirmed by experimental work set forth in the Declaration of Robert W. Bryant, Ph. D., Under 37 CFR § 1.132 (“Bryant Declaration”) accompanying applicants’ September 21, 2006, response. In particular, two groups of mice were tested for their aversion to denatonium and quinine, two bitter compounds, using a short access lickometer test, which measures the frequency with which the mice lick solutions containing varying concentrations of tastants. Bryant Declaration ¶ 6. The lick ratio of the wild type mice steadily decreased from 1.0 to 0.1 licks per interval as the concentration of denatonium increased from 0.1 mM to about 4 mM. *Id.* The lick ratio of the TRP8 knockout mice, however, did not fall below 1.0 until the denatonium concentration reached about 10 mM. *Id.* Similarly, the lick ratio of the wild type mice steadily decreased from about 0.7 to about 0.1 licks per interval as the concentration of quinine hydrochloride increased from 0.01 mM to about 10 mM. *Id.* The lick ratio of the TRP8 knockout mice, however, did not fall below 0.6 until the quinine hydrochloride concentration reached 1 mM, and never fell below 0.5. *Id.* Thus, the TRP8 knockout mice showed a decreased aversion to both bitter compounds compared to the response of the wild-type mice. *Id.* These data demonstrate that TRP8 is involved in bitter taste transduction. *Id.*

The present application also teaches that the level of TRP8 activation may be assessed, *e.g.*, by measuring membrane potential. Paragraph [0059]. The Bryant Declaration confirms that changes in membrane potential may be used to measure TRP8 activation. The effect of carbachol (a surrogate bitter tastant) on membrane potential in wild type HEK 293 cells and HEK 293 cells transfected with TRP8 was evaluated. Bryant Declaration ¶ 8. Carbachol activates the M1 G-protein-coupled receptor, leading to activation of TRP8, which in turn results in an increase in the fluorescence signal of a membrane potential dye. *Id.* This increased fluorescence signal is indicative of a decrease in the cell membrane potential caused by opening of a cation channel. *Id.* After exposure to 30  $\mu$ M carbachol, cells transfected with TRP8 exhibited an increase from 0 to about 70,000 fluorescence units. *Id.* This signal increase is indicative of cell depolarization where positive ions enter the cell and decrease the membrane potential. *Id.* In contrast, wild type cells exhibited very little change in fluorescence response and hence membrane potential. *Id.* These data demonstrate that membrane potential may be used to measure activation of TRP8. *Id.*

In view of the demonstration in the Bryant Declaration that TRP8 activation is involved in bitter taste transduction and that membrane potential can be used to measure TRP8 activation, it is apparent that an increase in the membrane potential of a cell expressing a TRP8 channel protein after exposure to a test compound would indicate that the test compound is a potential activator of TRP8, and, therefore, a potential inducer of bitter taste. Nothing more is required by the present claims.

For all of these reasons, the rejection of claims 37–40 for lack of enablement is improper and should be withdrawn.

The rejection of claims 37–40 under 35 U.S.C. § 112 (2<sup>nd</sup> para.) for indefiniteness is respectfully traversed, for substantially the reasons noted above with respect to enablement.

In view of all of the foregoing, it is submitted that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

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